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The first stage, the epidemiological survey was completed in November 1998 and, despite numerous problems associated with tracing the cohort members, achieved an overall response rate of 65.1%. The results of the epidemiological survey were published in January 1999,with four subsequent publications.

The second stage, the clinical study of 400 participants who completed the stage 1 questionnaire, lasted from December 1998 to September 2000. Of the 742 invited to attend, 343 (51.5%) visited the unit, 13.1% either cancelled or failed to show, with 26.4% refusing to participate.

The clinical study consisted of detailed medical, psychological and neuropsychological assessments lasting two days. Relevant biological samples were stored for subsequent immunological analyses, now completed. Detailed neurophysiological assessments were carried out in a sub sample. All these results are currently being analysed for later publication"

Based on the provisional finding of the second stage that there appears to be a change in the health of the study participants (see table 3) , funding has been obtained from the United Kingdom Medical Research Council for a follow up study of the stage 1 cohort. This will commence in January 2001.

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Summary

This is the third and final report of the study: A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces.

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Based on the provisional finding of the second stage that there appears to be a change in the health of the study participants (see table 3) , funding has been obtained from the United Kingdom Medical Research Council for a follow up study of the stage 1 cohort. This will commence in January 2001.

Study Outline

Background

This study was set up to address the prevalence of explained and unexplained illnesses and symptoms, in members of the United Kingdom Armed Forces who were deployed to the Persian Gulf during the Gulf War, and two comparison groups: those who had served in peace keeping forces in Bosnia, and a group who had served in neither theatre (Era controls).

Aims

This epidemiological study aimed to ascertain whether service in the Persian Gulf War by UK armed forces personnel was associated with an increase in physical and / or psychological morbidity compared to those who were not deployed or those deployed to Bosnia. Evidence was sought for an increase in known disorders, new or ill-defined conditions such as chronic fatigue syndrome, or an illness peculiar to Gulf War service.

The researchers also examined the self assessed effect of deployment related exposures such as pesticides, vaccinations and psychological trauma as well as pre morbid and psychosocial factors which may be implicated in such an increase. It was anticipated that this would identify avenues for further biological and psychosocial research.

Methodology

The epidemiological study of the prevalence of unexplained illnesses in the population at risk utilised a two stage design. Stage 1 was a questionnaire survey of 4250 Gulf War veterans selected at random, an equivalent sample of Bosnia Veterans and Era controls. The second stage involved the interview, examination and testing of a random sample (n=100 from each cohort) of the first stage participants who score above a cut off defining subjective ill health. A control group (n=100) of those with good health was also looked at.

The studies at stage 2 were intended to enable the team to assess the pattern of disorder in 'ill' returnees of all 3 cohorts in order to ascertain more precisely the pathogenesis of the disorder uncovered in stage 1.

Study Progress

Summary

The epidemiological survey and clinical studies were both completed, satisfying the requirements of the research grant.

Stage 1: Epidemiological survey

The problems associated with achieving a satisfactory response rate were fully detailed in the previous annual report. In summary, the problems were associated with receiving accurate addresses for the participants. Numerous tracing mechanisms

were employed to track the study member, and media appeals were made to encourage participation in the study.

The stage 1 mailing ceased on November 11th 1998, the final response rates shown in table 1.

Table 1 Final response rates to stage 1 questionnaire, after 3 mailings

	Bosnia N=4250		Era N=4248		Gulf N=4246		Overall N=12570	
	N	%*	N	%	N	%	n	
Yes[1]	***2620***	***(61.9)***	***2614***	***(62.9)***	***2961***	***(70.4)***	***8195***	***(65.1)***
RTS[2]	292	(6.9)	378	(9.1)	310	(7.4)	980	(7.8)
PR[3]	145	(3.4)	221	(5.3)	137	(3.2)	503	(4.0)
NR[4]	1173	(27.7)	945	(22.7)	796	(18.9)	2914	(23.1)
No address available	***20***		***90***		***42***		***152***	

[1] returned a completed questionnaire
[2] questionnaire "Returned to Sender"
[3] Participation in study refused
[4] Non Responder
* For the percentage calculations, the denominator has been adjusted by removing the n for no address available

Stage 1 publications

The key paper from the first stage was published in Jan 1999, where the health of the three cohorts, and associations with exposures was examined [1] .In addition, papers have been published investigating:

- the existence of a gulf war syndrome utilising factor analysis of the data [2]
- the association of vaccines and ill health [3]
- occupational risk factors for ill health in gulf veterans [4]
- chemical sensitivity and gulf veterans [5]

Under Review:

- Women in the 1991 Gulf war [6]
- Who gets Gulf war syndrome [7]
- A secondary factor analysis of symptoms [8]

Stage 2: Clinical study

Aim

The second stage commenced in December 1998 and was completed in September 2000. The aim was to conduct a battery of assessments on a total of approximately 400 individuals who had completed the stage 1 questionnaire.

Design

The design comprised of a **case comparison study**, where cases ("ill" participants) from the three groups were compared on the test batteries . At the same time, a **case control** study between the "ill" and "well" Gulf veterans was also made possible by a further cohort of 'well' Gulf returnees.

Definition of case / control

In the absence of a case definition for ill health in Gulf War Veterans, the value representing poorest decile for physical functioning (as measured by the SF 36) in the Era control group was applied across the three groups, creating the eligible sample of cases for invitation to the study. The control group (representing "well" participants) was stratified by perfect and middle health.

The clinical study comprised of two assessment schedules: Medical assessment and Neuropsychological assessment.

Medical Assessment

The medical assessment was be carried out by either the research nurse or doctor on the team. It lasted about 2 hours and covered the areas listed below.

In depth interview

An in-depth interview covering a detailed history of the participant's sociodemographic details, military history (deployments, trade, and length of service) life events, past health and current health status, lifestyles (alcohol, smoking)

Physical examination

Measurements were taken of height, weight, pulse and blood pressure. A standardised detailed neurological, musculoskeletal and dermatology assessment was performed. Pulmonary function tests were carried out using spirometry. Urinalysis was also performed.

Blood sample

A blood sample was taken for the following tests: full blood count, erythrocyte sedimentation rate, liver, renal and bone function, random blood sugar levels and thyroid function tests. Samples for genetic and immunological testing was also collected at the same time.

Psychiatric Interview

The Schedule for Clinical Assessment in Neuropsychiatry was used to generate Diagnostic and Statistical Manual-4th Edition diagnoses for psychiatric disorders.

Self completion questionnaires

The veterans were given self report questionnaires to measure quality of life, recall of Gulf specific exposures, post traumatic stress symptoms, social networks and fatigue .

Neuropsychological assessment

The neuropsychological assessment was carried out by one of the 2 research assistants on the team. It lasted about 2 hours. It involved a series of tasks which looked at various cognitive facets, as listed below.

General Functioning

Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981). Verbal subtests: Vocabulary, Digit Span, Arithmetic, Similarities; Performance subtests: Picture Arrangement, Block Design, Object Assembly;Digit Symbol
National Adult Reading Test, 2nd Edition (NART: Nelson, 1991)
Letter Number Sequencing task (WAIS III; Weschler, 1997)

Attention

Paced Auditory Serial Addition Task (PASAT: Gronwall & Wrightson, 1975)
Sustained Attention to Response Task (SART; Robertson et al, 1997)
Stroop Neuropsychological Screening Test (Trennery et al, 1989)
Trail Making Test, Parts A and B (Reitan, 1992)

Memory

Wechsler Memory Scales (WMS-R; Wechsler, 1987
Camden Recognition memory Tests (Warrington, 1996):

Motor Skills

Purdue Pegboard (Purdue Research Foundation, 1948):

Self Completion Questionnaires

Cognitive Failures Questionnaire (CFQ: Broadbent et al.1982)
Beck Depression Inventory (BDI: Beck & Steer, 1993)
State-Trait Anger Expression Inventory (STAXI – AX-EX: Spielberger, 1996
Mississippi Combat Related PTSD Scale (Keane et al, 1988) adapted for the GW;

Attendance figures for clinical study

In all, the team approached 742 participants to invite them to take part in the clinical study. Of these, 76 (10.2%) were untraceable and have been removed from the denominator for response rate calculation purposes.

The response and attrition (no show, cancellations) rates are shown for the four study groups in table 2. If a participant cancelled or failed to show, another was sampled from the eligible pool to replace them in an attempt to obtain the desired sample size of 400.

Table 2 Attendance rates across groups for clinical study

	Gulf Well		**Gulf Ill**		**Era Ill**		**Bosnia Ill**		**Total**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total Sent	182		196		245		119		742	
Untraceable	16	(8.8)	17	(8.7)	34	(13.9)	9	(7.6)	76	(10.2)
Adj. Total Sent [1]	**166**		**179**		**211**		**110**		**666**	
Attended	98	(59.0)	111	(62.0)	79	(37.4)	55	(50.0)	343	(51.5)
No show	4	(2.4)	7	(3.9)	11	(5.2)	8	(7.3)	30	(4.5)
Cancelled	17	(10.2)	9	(5.0)	24	(11.4)	7	(6.4)	57	(8.6)
Refused	38	(22.9)	39	(21.8)	72	(34.1)	27	(24.5)	176	(26.4)
Not responded	9	(5.4)	13	(7.3)	24	(11.4)	12	(10.9)	58	(8.7)
Died	0		0		1	(0.5)	1	(0.9)	2	(0.3)

[1] Adjusted Total Sent calculated by subtracting Untraceable from Total Sent

The overall response rate was 51.5%, with the highest being in the Gulf ill group (62.0%). The overall refusal rate was 26.4%, being highest in the Era ill group (34.1%). This was expected as it could be perceived that this group would feel that they had the least to gain from participating in a study looking at ill health in Gulf War veterans.

Results

The data from the medical assessment: psychiatric diagnoses (including post-traumatic stress), dermatological conditions and asthma, are being analysed and we anticipate that this will lead to peer reviewed publication in 2001. We have submitted the first papers with results from the neuropsychological assessment. [9,10]

Neuropsychological data

Case Crossovers

Due to the time lapse between filling out the postal questionnaire, and recruiting for phase 2 (12 –18 months), the SF36 was administered again when participants attended the unit for testing.

Table 3: Case Crossovers: Changes in health status between original recruitment and testing

ORIGINAL GROUP CLASSIFICATION	**MOST RECENT CASE CLASSIFICATION** Number of subjects	% of participants in same group originally
Gulf Well	131	88.8%
Gulf Ill	76	59.6%
Era Ill	39	50.0%
Bosnia Ill	36	66.7%

Table 3 shows that the majority of participants originally classified as Gulf Well are, according to the same criterion, still 'well', with only 11 becoming 'ill'. However 40% of the original Gulf Ill group are now classified as 'well', with fairly substantial crossovers in the Era and Bosnia groups too. Below we show preliminary analyses according to the current classification of the groups since we anticipate that current health perception will exert a major effect on cognitive functioning. Statistical analysis was carried out using SPSS.PC v8.

Key outcome measures

A 3 X 2 ANCOVA was used to compare the six groups on the test variables with deployment (Gulf, Era, Bosnia) and current health status (well, ill) as the factors. The analysis covaried for (i) age, education and NART-estimated IQ, and (ii) for these potential confounders plus BDI depression score. Least Significant Difference post hoc procedure (alpha set at 0.05 = ✓; X = non-significant) was used to identify significant differences between groups (see Table 4).

Group comparisons revealed an association between impaired physical functioning and symptoms of depression, post-traumatic stress disorder (PTSD), increased anger and subjective cognitive failures. Poorer performance on some general cognitive measures (such as performance IQ), and those of sequencing and attention was seen in association with being 'ill' but virtually all differences disappeared after adjusting for depressed mood. Deployment (to the Gulf *and* Bosnia) was also associated with symptoms of PTSD and *subjective* cognitive failures independently of health status as well as minor general cognitive (WAIS verbal IQ) and constructional impairment (the Purdue Assembly measure). Higher IQ and CFQ scores were associated with deployment to the Gulf and Bosnia while Purdue scores remained significantly poorer in the Gulf group alone even after adjusting for depressed mood (✓✓). The absolute levels of performance were within the normal or average range, e.g., mean VIQ (S.D.) Gulf ill = 94.6 (10.3); PIQ Gulf ill = 102.1 (13.7). There were no significant interactions between deployment and health status.

Table 4: Summary or neuropsychological testing results: Main effects of physical functioning on the SF-36 and Deployment (Gulf, Bosnia or Era).

Test	***Main Effects***	
	SF-36	**Deployment**
BDI	✓	X
Mississippi	✓	✓
STAXI –Trait anger	✓	X
CFQ	✓	✓✓
WAIS-VIQ	X	✓✓
WAIS-PIQ	✓	✓
Trails	✓	X
Stroop	X	X
PASAT	X	X
Attention/Vigilance	X	X
Learning/Memory	X	X
Purdue All	X	~
Purdue Assembly	X	✓✓

Conclusion

In conclusion, the results from our studies so far suggests that there is no objective neurocognitive deficit syndrome attributable to service in the Gulf war. Nevertheless, we have demonstrated that emotional and psychological disorder is common in GW veterans and, in a minority, likely to be clinically significant. Disturbances of mood probably lead to subjective underestimation of ability. Task performance deficits can themselves be explained to a large extent by depressed mood. Those weak effects which were detected were patchy in terms of the cognitive systems implicated. Furthermore they were just as likely to be attributable to any active deployment and hence not likely to be related to specific Gulf-related exposures – with the exception of the Purdue Assembly measure. Test performance in unwell veterans was impaired relative to well controls but generally within the normal range. However, reduced constructional ability on the Purdue Assembly sub-test cannot be explained in this way and could be an effect of Gulf-specific exposures. Such a specific deficit – other Purdue variables tending to be normal - defies an obvious pathophysiological

explanation. Further research of neuromotor coordination in Gulf War veterans would be valuable.

Problems encountered.

Tracing participants

The main problem encountered during the clinical study was the tracking of participants to invite to the Unit. Due to the passage of time, individuals have moved from the addresses supplied in their questionnaire. However, the expertise gained by the team in tracking the cohort members resulted in an overall untraceable rate of only 10.2% (see table 2). The Era cohort had both the highest rate of untraceable participants (13.9%), and also participants persistently not responding to the attempts made by the study team members to contact them (11.4%).

Non attendance / cancellations

As is usual with studies involving assessing study participants, there was a degree of non attendance and cancellations following provisional bookings. This seriously delayed the progress of the study, and necessitated extending the recruitment period beyond the initially envisaged 1 year. Due to the elongated period of testing, the life of the grant was extended by a further for months.

The breakdown of non attendance and cancellations by cohort is shown in table 2.

Staff Recruitment

For the clinical study, extra staff were recruited for the two assessment batteries:

Medical assessment:

Ms. Kate Davies (research nurse)

Neuropsychological assessment

Ms. Lydia Farrin (Research assistant)

Both team members left the team following the ending of the second stage, in September 2000.

Future planning

Stage 1 and 2 of the programme, funded by the DoD and the subject of this report, concluded in October 2000. Additional grant support has been received from the UK MRC for a stage 3 follow up of the cohort, which will commence in January 2001.

Follow up study

Based on the provisional finding of the second phase that there appears to be a change in the health of the study participants (see table 3) , funding has been obtained from

the United Kingdom Medical Research Council for a follow up study of the stage 1 cohort. This will commence in January 2001.

Peacekeeping study

This study includes a cohort of personnel who served in the former Yugoslavia. This affords the opportunity to assess the health of a cohort of peace keepers longitudinally, a subject which has increased in importance during the lifetime of the study.

Additional funding

1. **Specimens collection and storage** was funded by the United Kingdom Medical Research Council
2. **Immunological study:** A further grant from the DoD was obtained to enable testing of the Th1 / Th2 hypothesis. Data collection is completed, and preliminary results will be presented in January 2001
3. **Neuromuscular Symptoms Study:** A separate study of neurological, neuromuscular and neurophysiological symptoms was funded by the United Kingdom Ministry of Defence. Data collection is complete, and is currently being analysed.
4. **Autoantibodies**: Studies of autoantibody profile in GWV and CFS has been funded by the UK Linbury trust, and is complete.
5. **A UK / USA comparison study**: A multivariate analysis of symptoms in UK and US Gulf war veterans , has been funded by the Centre for Disease Control, USA. Data analysis is underway.
6. **UK Medical assessment Program (MAP):** The comparison of attendees and non attendees of the UK Medical Assessment Program for Gulf Veterans has been funded by the US Navy. The data is being analysed and will be presented in January 2001.

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Study Personnel

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i) Up to March 1997: Lieutenant Colonel John Graham
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* These positions were funded by the DoD grant.

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• Neuropsychology	Dr Til Wykes
• Immunology	Dr Mark Peakman, Ms Anja Skowera
• Neuromuscular symptoms study	Dr Michael Rose, Dr Mohammed Sharief

- Dermatology — Dr Anthony DuVivier
- Respiratory — Dr John Costello
- Combat Syndromes — Dr Edgar Jones

Publications list

Published or in press

1. Unwin CE, Blatchley N, Coker W et al. Health of UK servicemen who served in the Persian Gulf War. *Lance*t 1999;**353**:169-178

2. Ismail K, Everitt B, Blatchley N et al. Is there a Gulf War Syndrome? *Lancet* 1999; **353**:179-182

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Under review

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